over time could have altered any observed exposure–response associations. In addition, the authors did not indicate how assessments of individual children changed over time. If different children contributed to associations at different ages, the reported findings may not be indicative of a causal role for PBDEs. Notably, most associations were found at earlier ages, suggesting that even if PBDEs were causal, effects were reversible.

Herbstman et al. (2010) reported that all PBDEs were correlated with one another, as were repeated developmental scores. Yet associations varied both among PBDEs for the same tests and among repeated tests for the same PBDEs. If PBDEs are truly causal and acting via similar mechanisms of action, results should be repeatable across PBDEs and repeated tests. This is not the case, thus suggesting that chance or some other factor (e.g., alcohol, caffeine, poor diet, methylmercury, polychlorinated biphenyls) is a more likely explanation. In addition, all of the mothers in the study were pregnant and lived near the World Trade Center (WTC) on 11 September 2001. Given this proximity, there is no way of knowing whether other unmeasured exposures or other factors (e.g., psychological, behavioral) contributed to neurological effects.

Herbstman et al. (2010) used the Bayley Scales of Infant Development, Second Edition (BSID-II) to measure developmental impairment, which is based on a mean ± SD of 100 ± 15 to define normal development (Bayley 1993). This means that in 68% of the standard population, scores ranged from 85 to 115. The authors reported that through univariate analysis, the change in the BSID-II score from the 25th percentile of PBDE level to the 75th percentile was –5.57. This degree of change is well within the SD of the test, which makes it impossible to determine whether the relationship observed was due to PBDEs or simply the interindividual variability inherent to the test. Because the authors did not assess the association between PBDE levels and those scoring outside the SD of the test (compared with those scoring within), it is impossible to determine whether a clinically significant association between PBDE cord blood levels and developmental impairment exists. Changes in IQ scores are not very meaningful unless they are put directly into context with the scoring ranges in the test design; Herbstman et al. did not provide much information as to the scores that were actually produced, though they implied that those from mothers with higher PBDE levels were somehow impaired when they may well have been normal.

Taken together, these factors prevent an accurate assessment of whether prenatal exposure to PBDEs is associated with adverse neurodevelopmental effects.

*The views and opinions expressed in this article are those of the authors and not necessarily those of their respective employers.*

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### References

Bayley N. 1993. Bayley Scales of Infant Development. 2nd ed. San Antonio, TX:The Psychological Corporation.

Herbstman JB, Sjödin A, Kurzon M, Lederman SA, Jones RS, Rauh V. 2010. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect 118:712–719.

## Prenatal PBDEs and Neurodevelopment: Herbstman et al. Respond to Goodman et al. and to Banasik and Strosznajder

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In our article (Herbstman et al. 2010), we reported evidence showing that children who had higher cord blood concentrations of polybrominated diphenyl ethers (PBDEs) scored lower on tests of mental and motor development at 1–4 and 6 years of age. We initiated this work based on a large body of experimental research indicating that prenatal PBDE exposure has the potential to disrupt neurodevelopment. In their letter, Banasik and Strosznajder comment that the basis for our work may be biased because of experimental design flaws in the animal studies we cited. In the introduction of our paper, we cited an extensive review article in which Costa and Giordano (2007) carefully outlined a wide variety of toxicological evidence exploring the association between prenatal PBDE exposure and neurotoxicity. The authors cited both positive and negative animal studies and also reviewed *in vitro* studies and reports outlining endocrine-disrupting effects associated with PBDE exposure. We believe that we directed *EHP* readers to sufficient evidence that provides an adequate basis for our research question. Since our manuscript was accepted for publication, an additional *in vitro* study was published; that study (Schreiber et al. 2010) demonstrated that primary fetal human neural progenitor cells exposed to BDEs 47 and 99 had decreased migration distance and reduced differentiation into neurons and oligodendrocytes. Taken together, the scientific literature provides adequate biological plausibility and raises substantial concern about the potential for PBDE-related developmental neurotoxicity in humans.

Additional comments from Goodman et al. in their letter raise the possibility that the number of samples below the limit of detection (LOD) in our study sample could be higher than in the full study population and could thereby effect the results. We explored this possibility and found that the number of study samples with PBDE levels < LOD ranged from 14% to 19% for BDE-47, 40% to 50% for BDE-99, 27% to 34% for BDE-100 and 38% to 43% for BDE-153, depending on the testing age. These are not significantly different from the proportions of samples < LOD in the full study population.

Goodman et al. also point out that PBDE concentrations in our study were measured at one point in time and were likely to change over the course of pregnancy and postnatally. It is true that little is known about changes in PBDE levels within individuals over time or the half-lives of lower brominated PBDEs in human serum. One study (Geyer et al. 2004) estimated that that the half-lives of BDEs 47, 99, 100, and 153 range from 1.8 to 6.5 years We estimated prenatal PBDE exposure based on cord blood levels at delivery. If these estimated half-lives are accurate and we assume that PBDE exposure is chronic, it is unlikely that there are substantial changes in concentrations over an approximately 9-month pregnancy. Although cord blood is adequate for assessing PBDE exposure during the prenatal and early postnatal periods, which are critical periods for neuronal differentiation and migration, we concur that it is possible that there are other windows of susceptibility that are not adequately represented by cord blood PBDE concentrations (Rice and Barone 2000). In the "Discussion" of our article, we noted the limitation that we were not able to control for postnatal PBDE exposure in our analyses.

Goodman and al. ask whether different children contribute to the observed associations at different ages and assert that most associations were found at earlier ages, suggesting that observed effects are reversible. We reported that repeated developmental

test scores within an individual were correlated. We elected not to analyze the data using repeated measures because we used two different, age-appropriate neurodevelopmental tests. These tests are correlated but may not be directly comparable because they measure slightly different neurodevelopmental constructs. We disagree with the statement that associations were observed only at younger ages. Figure 1 of our article (Herbstman et al. 2010) illustrates that in our study population, the highest concentrations of exposure to prenatal PBDEs were associated with lower scores on nearly all neurodevelopmental tests at nearly all time points. Although many, but not all, of these point estimates are statistically significant, nearly all are in the same direction. Therefore, we cannot understand how this suggests that the effects of prenatal exposure are reversible.

Goodman et al. also posit that for correlated PBDEs to be causally associated with neurodevelopment, they must act via a similar mode of action (MOA). PBDE congeners are correlated, but they are of different chemical configurations and sizes. We believe that it is overly simplistic to assume that they operate via the same MOA, which is why we chose not to combine them into one exposure metric in our analyses.

Goodman et al. also raise the possibility that unmeasured confounders are a more likely explanation for the observed association between prenatal PBDEs and neurodevelopment, given that the study participants were pregnant and lived near the World Trade Center (WTC) on 11 September 2001 (9/11). Our study population consisted of women who delivered at hospitals located near the WTC; only one-fourth of our study population actually lived within 2 miles of the WTC. As we stated in our article, we cannot rule out the potential impact of unmeasured confounders. This problem is not unique to our study. Our study population is distinctive in that the participants were identified to explore the effects of prenatal exposure to the WTC after 9/11. Although we measured and controlled our analyses for many potential confounders, we cannot rule out the possibility that some unmeasured factor could be associated with both prenatal PBDE exposure and neurodevelopmental test scores and could have thereby confounded the observed associations. However, we do not understand the basis by which Goodman et al. conclude that unmeasured confounders are a more likely explanation.

Finally, Goodman et al. assert that it is impossible to determine the clinical significance of the reported associations between prenatal PBDE levels and neurodevelopmental test scores because the observed differences between exposure groups are smaller than the SD of the test instrument on a standardized population [for the Bayley Scales of Infant Development, Second Edition (BSID-II), SD = 15). We believe that Goodman et al. misinterpreted the scores derived from the Bayley scales in the context of population research. It is true that the distribution of the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores have a mean ± SD of 100 ± 15 (Bayley 1993); this is a useful guideline for interpreting the score for an individual child such that a child who scores < 1 SD of the standardized mean (score < 85) can be clinically classified as having "delayed performance." However, the differences we noted in our article represent average difference in test scores between groups of children characterized based on their exposure levels. To illustrate our point, for BDE-100 at 36 months of age, the average test score for the highly exposed group is 6.1 points lower than the average score for the group of children with lower exposure (controlling for confounders). This shift is both statistically significant and, if confirmed, biologically relevant on a population level. Furthermore, the magnitude of this effect may be cognitively and educationally meaningful, as has been illustrated in the lead literature, where the size of the adverse effect is similar.

Our study was a well-conducted, prospective, longitudinal cohort study that demonstrated associations between prenatal PBDE exposure and adverse neurodevelopment. Given that this is the first study to report these associations in humans, we interpreted these results cautiously until they can be replicated in another study population.

*The authors declare that they have no actual or potential competing financial interests.*

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## Errata

In the review by Rohr and McCoy [Environ Health Perspect 118:20–32 (2010)], Orton et al. (2006) was cited on page 26 but was not included in the reference list. The reference is as follows:

Orton F, Carr JA, Handy RD. 2006. Effects of nitrate and atrazine on larval development and sexual differentiation in the northern leopard frog *Rana pipiens*. Environ Toxicol Chem 25:65–71.

Cao et al. [Environ Health Perspect 118:1332–1337 (2010)] have reported errors in their paper. On page 1333 in the second paragraph of "Statistical methods and data analysis," the following sentence was omitted:

Because length, weight, and head circumference were highly correlated with age (the pairwise Pearson correlation coefficients were 0.91, 0.84, and 0.83, respectively), they were not included in the model, but we combined length and weight as body mass index (BMI) and introduced it into the model.

In the fourth paragraph of that section, one of the covariates (BMI) was omitted. The corrected sentence is as follows:

These covariates were age, sex, BMI, urinary thiocyanate, urinary nitrate, and urinary iodide.

In addition, in the footnote of Table 3, "LOD/16%" was incorrect. The corrected sentence is as follows:

Adjusted for age; values < LOD were replaced by LOD/$\sqrt{2}$; 16% for perchlorate; 0% for iodide; 6% for thiocyanate; 14% for nitrate. Mixed linear models account for multiple measures in the same child.

In the editorial by Fontham and Trapido [Environ Health Perspect 118:A422–A423 (2010)], one reference cited in the text was inadvertently omitted from the reference list. The reference for Grulich et al. (2007) is as follows:

Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. 2007. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 370(9581):59–67.

*EHP* apologizes for the error.

## References

Bayley N. 1993. Bayley Scales of Infant Development. 2nd ed. San Antonio, TX:The Psychological Corporation.

Costa LG, Giordano G. 2007. Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. Neurotoxicology 28(6):1047–1067.

Geyer HJ, Schramm KW, Darnerud PO, Aune M, Feicht EA, Fried KW, et al. 2004. Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans. Organohalogen Compounds 66:3867–3872.

Herbstman JB, Sjödin A, Kurzon M, Lederman SA, Jones RS, Rauh V, et al. 2010. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect 118:712–719.

Rice D, Barone S. 2000. Critical periods of vulnerability for the developing nervous system: evidence from human and animal models. Environ Health Perspect 108(suppl 3):511–533.

Schreiber T, Gassmann K, Götz C, Hübenthal U, Moors M, Krause G, et al. 2010. Polybrominated diphenyl ethers induce developmental neurotoxicity in a human *in vitro* model: evidence for endocrine disruption. Environ Health Perspect 118: 572–578.